REMARKS

Initially, Applicant notes with appreciation that the rejection of claims 382-388 under 35 U.S.C. §112, first paragraph, has been withdrawn. Before turning to the second paragraph technical rejection of claims 383, 384, 391 and 394, Applicant believes that it is important to clarify several matters of terminology relating to cell biology in order to accord proper construction to Applicant's claims. Specifically, the Examiner, in determining the scope of the claimed invention, has erroneously construed several essential medical terms in a manner that has prevented a proper and meaningful analysis of the claimed subject matter. Applicant presents the following discussion and supporting evidence in regard to the medical terminology employed in the specification and claims, as used by those skilled in the medical art, in a sincere effort to establish a fair and reasonable construction of the claims in issue.

Firstly, the Examiner's statement, at page 3 of the Final Rejection (hereinafter "Final"), that all pluripotent cells are stem cells, is not correct. The article published by the University of Pittsburgh Medical Center on bio.com entitled, "Discarded Placentas Deliver Researchers Promising Cells Similar to Embryonic Stem Cells" (attached hereto as Exhibit A) constitutes convincing objective evidence regarding certain cells that exhibit pluripotent characteristics which are not stem cells.. This publication identified amniotic epithelial cells as having the potential to differentiate into many different cell types, thus having pluripotent characteristics. Amniotic epithelial cells are not stem cells; and, therefore, the Examiner's broad statement is erroneous.

Secondly, the Examiner's statement, at page 4 of the Final, that all stem cells are at least

pluripotent, likewise is not correct. While it is true that germinal cells are pluripotent and that embryonic stem cells are pluripotent, it is well established in the medical art that there are stem cells which are not pluripotent. The NIH definitions cited as Exhibit C in Applicant's August 2, 2005 response indicate that there are unipotent cells (stem cells). Moreover, the Wikipedia encyclopedia (attached hereto as Exhibit B) evinces that the term unipotent cell: "in cell biology, is used to describe a cell (e.g. a stem cell) which has the capacity to develop/differentiate into only one type of tissue/cell type." Applicant further directs the Examiner's attention to the MJA (The Medical Journal of Australia) publication authored by Byrne et al. in 2003 entitled, "Stem Cell Therapies: A Tale of Caution" (attached hereto as Exhibit C) which identifies unipotent stem cells as comprising stem cells that are committed to development into one cell type and describes attempts to reconstitute skeletal muscle as comprising a form of unipotent stem cell therapy (emphasis added). In view of the above evidence, there can be no question that the Examiner's determination that "all stem cells are at least pluripotent" is misplaced and lacks evidentiary support in this record.

Thirdly, the Examiner has erroneously posited, at page 14 of the Final, that, "There is no such thing as a unipotent stem cell." The Examiner is again referred to the above-mentioned evidence in regard to such error. The Examiner has not submitted any contradictory evidence.

Fourthly, the Examiner has mistakenly asserted, at pages 6 and 7 of the Final, that the art simply does not use the term "multifactorial" and "non-specific" with reference to cells. Such assertion is not correct. Applicant points out that the use of such terminology may be found in the instant specification in identifying growth factors, e.g., cells that induce/promote the growth of composite soft tissues. Inasmuch as Dr. Elia appears to be the first inventor to recognize such

cell characteristics in the field of regenerative medicine, it is not surprising that others did not use such terminology prior to Dr. Elia's invention. In this regard, Dr. Elia used such term to describe growth factors, including cellular growth factors, in his 1993 parent application. Usage of the terminology may be found in the medical art subsequent to Dr. Elia's filing date, as the field continues to expand, as evident from the record of the instant application. Such usage is documented in the following detailed discussion of the 35 U.S.C. §112, second paragraph, rejection which follows. The Examiner is referred to such discussion.

Claims 383, 384, 391, 393, and 394 stand rejected by the Examiner under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter, which Applicant regards as the invention. Specifically, the Examiner opines that, "[s]ince neither the specification nor the prior art provide a definition of multifactorial and non-specific cells, the metes and bounds of the claims cannot be determined and they are indefinite...". Applicant disagrees that the claims violate the definiteness requirement of Section 112 of the statute.

Applicant directs the Examiner's attention to the recent *en banc* decision of the CAFC in Phillips v. AWH Corporation, 03-1269-1286, decided July 12, 2005. While the Phillips case involved patent claim infringement, Applicant believes that the principles and authorities expressed in this case are equally applicable for providing guidance to the Patent and Trademark Office (hereinafter "PTO") in determining the meaning of terms in the specification and claims of a pending patent application.

The Phillips decision indicated that the claims of a patent are generally given their ordinary and customary meaning in the art, citing the Vitronics v. Conceptronic, Inc., 90 F. 3d

1582 (Fed. Cir. 1996). Also cited was the Multiform Desiccants, Inc. v. Medzorn, Ltd. Decision, 133 F. 3d 1473, 1477 (Fed. Cir. 1980) for the principle that claims should be read in the context of the patent. The Court in Phillips further observed that extrinsic evidence is less significant than the intrinsic record in determining the legally operative meaning of claim language, citing C.R. Bard, Inc. v. U.S. Surgical Corp., 388 F. 3d 858, 862 (Fed. Cir. 2000). The Court in Phillips also stated that dictionary evidence can be useful in claim interpretation, but that such evidence is less reliable than the patent specification and its prosecution history. Applicant submits that the Examiner should interpret the words "multifactorial" and "non-specific" in light of the specification as would be apparent to a person skilled in the medical art and thus give such words their ordinary meaning in the art to which the invention pertains. A different interpretation, such as that foisted by the Examiner, bottomed on non-contextual sources, places the term out of context and thus clearly would not be entitled to the same evidentiary weight as the interpretation by a skilled person in the medical art of Applicant's disclosure.

In the instant prosecution, the Examiner attempts to support her reasoning by a lack of success in regard to search results regarding these terms, followed by a series of suppositions and speculations regarding the meaning of these terms. Applicant believes that the Examiner's position amounts to no more than opinion because no objective evidence related to the medical art is presented. Moreover, the Examiner's position appears to be taken from a chemist's perspective, not from the perspective of one skilled in the medical art reading the instant specification. Had the Examiner viewed the term "factor" as a skilled medical person rather than a chemist, she would have then understood the term in the context of the medical art and would not have raised an issue of indefiniteness. The meaning of the term "factor" is well known in the

medical art, and one skilled in such art would have no difficulty understanding this term. Obviously, one understanding the medical term "factor" would also understand the term "multifactorial" to mean "more than one factor."

The Examiner is reminded that Applicant previously located and filed relevant search evidence in the Fifth Supplemental Information Disclosure Statement ("IDS") filed on October 21, 2004 (via fax) regarding the definitions of the terms. Apparently, the Examiner failed to locate Applicant's above-mentioned evidence in her search. In any event, the definitions of "multifactorial" and "non-specific" presented in the IDS provide confirming evidence that the disputed terms are known and used properly in Applicant's specification. Note further that the IDS identifies these term as adjectives.

Applicant also conducted a search of the NIH Medical Dictionary and found the following definitions in Merriam Webster's Medline Plus Medical Dictionary (attached hereto as Exhibits D and E):

Factor:	***(noun)*** A substance that functions in or promotes the function of a particular physiological process or bodily system.
Multifactorial:	***(adjective)*** Having, involving, or produced by a variety of elements or causes.

Thus, the noun "factor," as used in Applicant's specification, means a substance, such as a cell, that promotes a particular physiological process, such as the formation of a bud and subsequent growth of soft tissue. "Multifactorial" is an adjective used to denote a quality of a cell. A cell is deemed to be "multifactorial" when a variety (more than one) of elements (factors)

promote the growth of soft tissue. Accordingly, there can be no doubt that the term "multifactorial" is used properly in the specification, and that its meaning would be clear to one skilled in the medical art. The above-mentioned definitions are consistent with Applicant's specification, with the materials furnished in the IDS, and with the use of this term by those skilled in the medical art, as further explained below.

Applicant notes that the terms were understood by skilled persons in the art, i.e., by Drs. Heuser and Lorincz, in paragraph 7 of their Second Supplemental Declarations (of record in co-pending Application Serial No. 09/794,456). Such Second Supplemental Declarations are attached hereto as Exhibit F. It is noted that the Examiner, at pages 6 and 11 of the Final, considered that Applicant's prior reference to declarations of Drs. Heuser and Lorincz did not indicate specific declarations or sections thereof. The Examiner's point is well taken because Applicant, through a clerical error, inadvertently believed that declarations of Dr. Heuser and Lorincz relating to the "multifactorial and non-specific" terminology were of record in the instant application. Such error is regretted. Applicant notes with appreciation that the Examiner, at page 11 of the Final, pointed out that the above-discussed declarations were submitted in related applications and that Applicant "may submit them in response to the instant office action and they will be considered at that time." Applicant appreciates the Examiner's courtesy and hereby submits the above-mentioned Second Supplemental Declarations for the Examiner's consideration.

Additionally, an understanding of the questioned terms by workers skilled in the medical art consistent with the description in Applicant's specification, the definition of "multifactorial" in the IDS, and the NIH Medical Dictionary (above-mentioned Exhibits D and E) can be found

in the 2005 publication of Strauer et al. entitled, "Regeneration of Human Infarcted Heart Muscle by Intracoronary Autologous Bone Marrow Cell Transplantation in Chronic Coronary Artery Disease" (hereinafter referred to as "Strauer 2005" and attached hereto as Exhibit G). In Strauer 2005, Dr. Strauer states at page 1656, second column, third paragraph that, "The regenerative potential of bone-marrow-derived stem cells may be explained by any of four mechanisms." These four-cell biologic and molecular mechanisms are further described as "factors" at page 1657, second column, second full paragraph. Therefore, it is clear to a skilled person in the medical art that Dr. Strauer and his co-authors identify the regenerative potential of bone marrow stem cells as being derived from at least four different mechanisms/factors or characteristics of such cells. It follows that bone marrow stem cells can be appropriately styled as four-factor cells, i.e., multifactorial. This description of said term is consistent with the disclosure of the instant application, with the definitions in above-mentioned Exhibits D and E, with the definitions submitted in the IDS, and with the above-mentioned understandings of Drs. Heuser and Lorincz. Thus, Strauer 2005 confirms that another skilled group of medical experts possesses an understanding of "multifactorial" cells that is consistent with that of Applicant and the evidentiary materials discussed herein.

The Examiner's attention is also directed to another publication in which a skilled medical person utilizes the term "multifactorial" in a manner consistent with Applicant's specification and the above-mentioned other skilled persons; namely, the 2001 publication of Caplan et al. (hereinafter "Caplan") entitled, "Mesenchymal stem cells: building blocks for molecular medicine in the 21st century" (attached hereto as Exhibit H). Note the use of the term "multifactorial" in this publication. Caplan teaches that mesenchymal stem cells prevalent in

bone marrow are pluripotent in that they are capable of differentiating into multiple tissues types. Caplan further teaches that such bone marrow stem cells undergo a multifactorial differentiation pathway from stem cells to functional tissues including elaborate composite tissues *in situ*. This usage is consistent with Applicant's use of the terms "multifactorial" and "non-specific" to define pluripotent cells such as bone marrow stem cells and germinal cells, which induce or promote the growth of composite soft tissues.

Certainly, Applicant's above-mentioned evidence, when considered with the authoritative statements and precedential tenets of Phillips, should be accorded greater evidentiary weight than the Examiner's unsuccessful search attempt and unsubstantiated speculation as to the intended meaning of the questioned term.

In summary, when following the Phillips decision and when reading the claim language within the context of the specification with the understanding of a person skilled in the medical art, Applicant believes that there can be no question as to the meaning of "multifactorial." The meaning of "non-specific" as being synonymous with "non-specialized" is apparent from previous submissions. Accordingly, the indefiniteness rejection should be withdrawn.

Applicant submits that the Examiner also erred in concluding that claims 383 and 384 are contradictory. Claim 383 requires "multifactorial and non-specific cells". Claim 384 further limits claim 383 by reciting that the cells are "stem cells." The specification at page 37 describes stem cells and germinal cells as included in the class multifactorial and non-specific. Accordingly, it requires no more than a basic understanding of patent claim construction to conclude that claim 384 is in full compliance with the fourth paragraph of Section 112. Further, it is noted that the Examiner's statement on page 10 of the Final that, "The specification states,

"Multifactorial and nonspecific cells (such as stem cells...) ..." Such implies that all stem cells are multifactorial and nonspecific, in direct contradiction to Applicant's arguments." This statement is not correct. The Examiner appears to have misquoted Applicant's specification. As can be evinced from the complete disclosure on page 37 of the specification, Applicant describes "stem cells and germinal cells" (emphasis added) as being exemplary of "multifactorial and non-specific cells." Claim 394 is deemed proper since it further limits claims 393 and 391, from which it directly and indirectly depends. Such limitation is proper because claim 391 broadly includes both single factor and multifactor cells, and dependent claim 393 further limits such cells to multifactorial cells.

In summary, Applicant believes that once the Examiner's understanding of the questioned terminology is transformed into an understanding consistent with that used by a skilled person in the medical art, there should be no further indefiniteness question remaining. Applicant hereby repeats the remarks (and associated evidence) that were presented in the August 2, 2005 response. These remarks are not incorporated into the instant response so as to not burden the record; however, such remarks are consistent with the above remarks and are maintained and deemed to be persuasive. Applicant submits for all of the above reasons that claims 383, 384, 391 and 394 are in compliance with the definiteness requirement of the statute and that the Examiner's rejection should be withdrawn.

Claims 382-394 were rejected under 35 U.S.C. §102(b) as anticipated by Lutjen. Applicant disagrees that Lutjen constitutes anticipatory prior art within the purview of Section 102. Favorable reconsideration of this rejection is requested in view of the following remarks and accompanying evidence.

It is trite law that in order for a prior art reference to be considered as anticipatory under Section 102 it must teach each and every limitation of the claimed invention. Applicant, of course, is cognizant that the courts have interpreted Section 102 to cover prior art references, which teach all claimed elements either expressly or inherently. Under either circumstance, anticipation is a question of fact, and it is well-understood law that the Examiner must provide a reasonable factual basis to support a rejection for anticipation under Section 102.

The Examiner did not separately treat the claims; rather, the Examiner opined that Lutjen teaches each method step of each claim in the instant specification. Specifically, the Examiner states that, "Lutjen teach a method for producing an[d] integrating a desired soft tissue (an artery) at a selected site in a body of a human patient (in the uterus of a human patient) comprising placing cells (the two-cell embryo) in said body of said human patient (the uterus is in the body), forming a bud (such as a limb bud) at said selected site (inside the uterus) in said body of said human patient, and growing and integrating said desired soft tissue (artery) in said body of said human patient from said bud." The Examiner further opines that, "a fetus and all its parts, are integrated into a body of a human patient." (Final, page 21).

Firstly, the Examiner's position is bottomed on an incorrect interpretation of the claimed limitation of "integrating" as used and intended by Applicant in describing the claimed invention. Following the precedent of Philips, it is incumbent upon the Examiner to read the claim limitations in the context intended in the specification. It is patently clear from Applicant's specification that the grown soft tissue is permanently integrated into the patient's body. See, in particular, page 54 wherein is disclosed that a new artery is grown adjacent the patient's original artery and "has integrated itself" with the original artery and page 56 wherein the newly grown

artery is disclosed to "integrate itself in the heart." Also see page 45 wherein is disclosed that an artery can be grown in the heart, legs, or other areas by injecting genetic material (cells) into muscle at a desired site, and that a damaged portion of a heart can be used as a matrix while the new muscles and vessels grow. Also see the disclosure at page 46 where it is disclosed that the newly grown muscle may integrate itself into the existing muscle. It is clear from such disclosure that the limitation "integrate" as used in the specification and claims at issue defines permanently integrating the grown soft tissue into the patient's body. This is the precise contribution that Applicant has made to the therapeutic medical art. This is the definition and meaning that one skilled in the medical art reading the specification and claims, in proper context, would give to the "integrating" language of the claims. See Philips, supra.

When viewing the claims in the above light, it is patently clear that an unborn fetus is not integrated into the patient's body. Stedman's Medical Dictionary, relied upon by the Examiner for a definition of "placenta," provides evidence that a fetus is not integrated into the mother's body by its statement that there is "no direct mixing of fetal and maternal blood, but the intervening tissue (the placental membrane) is sufficiently thin to permit the adsorption of nutritive materials..." Further, Stedman's later defines "percreta" as a condition that occurs when the placenta does integrate with the uterus resulting in a catastrophic rupture of the uterus. An ectopic pregnancy is another well-known example of a medical condition where the fetus integrates with the mother and results in a catastrophic event. Both of these events result in termination of the fetus. It is patently clear from such evidence that the Examiner's assertion (Final page 21) that, "a fetus, and all of its parts, are integrated into to [sic] body of a human patient" lacks sound factual basis. Should any such harmful integration have occurred in Lutjen,

it would not have been possible for the baby to be born. Thus, Lutjen did not "integrate" the fetus into the woman. Perforce, it cannot reasonably be said that Lutjen responds to the "integrating" limitation of the claims.

Applicant believes that the Examiner's statement that none of the claims exclude totipotent cells is misplaced. The scope of a claim is determined by the limitations expressly contained therein. Further, the Examiner's statement that claims 382, 385, 387 and 388 do not place limitations on the cells is lacking in merit because in each instance the claims require a class of cells that induce the growth of soft tissue, which integrates with the patient's body. If particular cells, for example, are unipotent or, in the case of Lutjen are totipotent, such cells are incapable of growing and integrating an artery in the patient's body (claims 385, 388) and are therefore excluded from the claims. The Examiner's attempt to hold the claim language indefinite and at the same time consider the subject matter defined by such language to reasonably read on Lutjen's two-cell embryo is derogating to the record and current law.

The Examiner's statement that totipotent cells are stem cells is not correct. The May 2000 NIH publication entitled, "Stem Cells: A Primer" (attached hereto as Exhibit I) defines stem cells as "cells that have the ability to divide for indefinite periods in culture and to give rise to specialized cells." While Lutjen's two-cell embryo is a totipotent cell – meaning that its potential is total in that it can give rise to an entire human organism – it is not a stem cell because it does not have the ability to self-renew *in vitro* virtually indefinitely. This definition is consistent with the definition for "stem cells" contained in above-discussed Exhibit A. Such totipotent cell specializes to form a blastocyst the inner cell mass of which specializes into pluripotent cells. Pluripotent cells are not totipotent because their potential is not total, and they

are not embryos. In addition, pluripotent cells do not form a placenta. This publication makes it clear that if an inner cell mass cell, i.e., an embryonic stem cell, were placed in a woman's uterus, it would not develop into a fetus. It is again emphasized that while it is clear to those skilled in the medical art that pluripotent cells are incapable of forming a placenta, pluripotent cells can be harvested from placenta tissue. The Examiner has not provided any evidence to support her position that an embryonic stem cell is considered to be totipotent in the medical art. Thus, it is patently clear that the two-cell embryo employed by Lutjen does not respond to the cell required in Applicant's claims for "growing and integrating" desired soft tissue in the patient's body. This is especially true for the "multifactorial and non-specific" cell required by claim 383, the stem cells required by claims 384, 389, and 393, and the "pluripotent cells" required by claim 391. Applicant's specification and claims do not broadly describe using an embryo, and Applicant's disclosed invention would not be operable using such a cell. Nor would the implantation of an embryonic stem cell in the uterus of a female produce the results described by Lutjen. The Examiner's statement that the claims do not require that the implanted cells be unable to form a placenta is considered to be inapt. The claims, by reciting "growing and integrating said desired soft tissue in said body of said human patient," preclude the formation of a placenta and fetus. Accordingly, it cannot be reasonably concluded that the two-cell embryo used by Lutjen responds to the cellular growth factors required in Applicant's claims nor can it be reasonably concluded that the fetus resulting from Lutjen's fertilization implantation responds to the "integrating" limitation of the subject claims. It is patently clear that the claimed subject matter requires a different implant material and a claimed result that is distinct from that described by Lutjen.

Applicant hereby repeats the remarks (and associated evidence) that were presented in the August 2, 2005 response. These remarks are not incorporated into the instant response so as to not burden the record; however, such remarks are consistent with the above remarks and are maintained and deemed to be persuasive.

Although Applicant believes that the Section 102 rejection should be withdrawn for the reasons set forth above, the following additional points raised by the Examiner in the Final will be addressed in a sincere attempt to clarify the record. The Examiner has mischaracterized the cited Fukuda et al. (hereinafter "Fukuda") reference as being exemplary of the prior art's considering embryonic stem ("ES") cells to be totipotent in an attempt to support her statement that ES cells are totipotent (Final, page 16). Both are incorrect. Fukuda teaches that, "ES cells are derived from the inner mass of the preimplantation blastocyst" (page 1273) and ES cells are pluripotent (page 1275). Fukuda further teaches that ES cell lines require the destruction of embryos (page 1278). Fukuda also teaches that adult bone marrow is pluripotent (page 1278). Thus, rather than support the Examiner's position, Fukuda is evidence of the correctness of Applicant's specification in regard to the disclosed and claimed cellular growth factors.

The Examiner's reliance on Satoh et al. (hereinafter "Satoh") is not well placed. Satoh teaches that pluripotent hematopoietic stem cells are defined as cells capable of both self-renewal (i.e., stem cells) and multilineage differentiation (i.e., pluripotency). This clearly corresponds to Applicant's statement that pluripotent cells can promote the growth of all three major soft tissue types i.e., are capable of multilineage differentiation. That Satoh found that hematopoietic stem cells were virtually confined to lymphoid lineage (were non-pluripotent) does not invalidate

Applicant's statement. Further, the Examiner's use of Satoh (Final, page 16) to establish that not all pluripotent cells are also totipotent is akin to using a negative to prove a positive.

On page 18 of the Final, the Examiner challenges Applicant's statement that totipotent cells are considered "master cells" since they have the potential to form an entire organism, which, by the way, corresponds to the NIH's description of totipotent cells (above-discussed Exhibit I). The relevance of the Examiner's citation of Alberts et al. to support her conclusion that, "What determines whether a cell is a neuron or a keratinocyte or a hematopoeitic cell or a totipotent cell or any cell type is the control of expression of the genome" is not understood. If the Examiner is contending that it is known to use any cell type through control of expression of the genome to produce a human organism, she has not provided evidence of this. In any event, the Examiner has not explained the nexus between such bogus reasoning and the anticipation rejection in issue. Dr. Elia has maintained throughout the prosecution of this invention that his disclosure and claims do not include the use of totipotent cells since such cells would not provide the claimed desired therapeutic effect.

Applicant submits that claims 382-394 define novel subject matter within the purview of 35 U.S.C §102, and favorable reconsideration of this rejection of record is respectfully requested.

Applicant again points out that the instant application has been pending since 1998, is entitled to Special Status during prosecution, and is subject to term erosion. Accordingly, Applicant believes that prosecution of this case should proceed as quickly and as timely as possible. To this end, Applicant has provided extensive evidence that should conclusively resolve all outstanding issues and result in the allowance of the application. Applicant believes the Examiner should consider and interpret the disclosed and claimed terminology in a manner

consistent with evidence submitted by Applicant (regarding how such terminology is understood and used by those skilled in the medical art) and then apply such terminology to the instant claims. The scope of the claims would then be interpreted in terms understood and used by those skilled in the medical art. Should the Examiner continue to maintain the rejections herein, all evidence submitted herewith (Exhibits A –I) should be entered in the record because such evidence was invited by the Examiner, and was necessitated by and responsive to new points raised and new evidentiary materials cited by the Examiner, for the first time, in the Final. Moreover, entry of such evidence certainly would preserve Applicant's rights to due process and result in a reduction of the number of issues to be resolved in an appeal.

From the foregoing remarks, Applicant submits that the instant application is in condition for allowance, and a Notice to such effect is respectfully requested. Should the Examiner have any questions or require additional information or discussion to place the application in condition for allowance, a phone call to the undersigned attorney would be appreciated.

Respectfully submitted,

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